REMARKS

The amendments to the specification amend the priority claim added by amendment by the Preliminary Amendment dated August 30, 2001.

The amendments to the claims find support in the application as originally filed. The amendments to claims 1-4, 9, 14, and 16 delete terms and amend the description of the heregulin fragments, finding support, for example, at page 12, lines 33-35, and elsewhere in the specification and claims as originally filed. The amendments to claim 6 find support in the application at page 4, lines 9-20; at page 12, lines 24-26 and 33-39; at page 20, lines 30-36; at page 45, lines 33-37; and elsewhere in the specification, figures, and claims as originally filed. The amendments to claims 19-21 take into account that the initiating Met in heregulin-β1 (HRG-β1) is Met 31 as disclosed in the specification, for example, at page 5, lines 1-3, and the amino acid residues are thus shifted by 30 as recited in the amended claims 19-21.

Support for new claims 22-24 is found in the specification, for example, at page 46, lines 32-40; at page 49, lines 26-30; in original claim 12; and elsewhere in the application and claims as originally filed. The new claims are directed to the methods of claims 1, 6, and 11, with the further specification that the inner-ear-supporting cell recited in the claim is in the cochlea. New claims 22-24 are believed to be novel and non-obvious over the art.

No new matter is added by way of the amendments to the specification or to the claims.

Claims 1-12, 14-17 and 19-21 are pending in the application, and stand rejected.

Claim 6 stands rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. 6,017,886 to Carnahan (hereafter "Carnahan"). Claims 1-5, 7-12, 14-17, and 19-21 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Claim 9 stands rejected under 35 U.S.C. §103(a) as allegedly obvious over Carnahan in view of U.S. Patent 5,587,458 to King (hereafter "King"). Claim 11 stands rejected under 35 U.S.C. §103(a) as allegedly obvious over Carnahan in view of Carroway *et al.*

(hereafter "Carroway"). Claims 1-5, 7, 8, 10-12, 14-17, and 19-21 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Carnahan in view of U.S. Patent 5,367,060 to Vandlen *et al.* (hereafter "Vandlen").

Applicants respectfully traverse the claim rejections.

Priority

Applicants note that although a Preliminary Amendment noting the proper priority was filed in this case on August 30, 2001, that amendment is not reflected in the published application nor on the Filing Receipt. Applicants further note that the transmittal letter accompanying the application on May 4, 2001 (the day the application was filed) stated that the application claimed the benefit of priority of PCT/US99/25744, filed October 28, 1999, which claims the benefit of priority from U.S. Provisional Serial No. 60/107,522, filed November 7, 1998. In that same transmittal letter the prior applications were incorporated by reference. Accordingly, since the priority claim and the incorporation by reference statement were made on the filing date, they were effective and proper, and the amendment of the specification to cite this priority is also proper.

However, inspection of the PAIR system records and of the Filing Receipt indicates that the USPTO does not correctly note the priority of this application. Applicants hereby again request correction of the filing receipt for this application to correctly reflect the priority claim made at the time the application was filed.

The Rejections of Claims 1-5, 7-12, 14-17, and 19-21 under 35 U.S.C. §112, second paragraph

Claims 1-5, 7-12, 14-17, and 19-21 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse these rejections.

The Examiner discusses variants and fragments, suggesting that the limitation "said fragments comprise amino acids numbered 226-266 of the corresponding

heregulin sequence" in claims 1, 14, and 16 is unclear. However, the subject phrase standing deleted without prejudice in the present amendment, the rejections of claims 1-5, 7-12, 14-17, and 19-21 under 35 U.S.C. §112, second paragraph as allegedly indefinite are believed to be moot.

Applicants note that the specification states at page 5, lines 1-3, that the initiating Met for heregulin-β1 (HRG-β1; SEQ ID NO: 3) is at position M31. Accordingly, and in view of the USPTO's comments on page 6 of the instant Office Action, claims 19-21 have been amended to clarify what was meant by the phrase "of the mature polypeptide within SEQ ID NO: 3" in these claims as originally filed by specifying the amino acid residues suitable for substitution within SEQ ID NO: 3.

Thus, the Applicant respectfully submits that the rejections to claims 1-5, 7-12, 14-17, and 19-21 as allegedly indefinite under 35 U.S.C. §112, second paragraph are overcome.

The Rejection of Claim 6 under 35 U.S.C. §102(e)

Claim 6 stands rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 6,017,886 to Carnahan (hereafter "Carnahan"). Carnahan discusses a hybrid peptide (Carnahan SEQ ID NO: 1, shown in Fig. 1 and listed at column 2, lines 5-10 of that reference) and its effects; the USPTO has characterized this hybrid peptide as a "recombinant human heregulin peptide or fragment thereof" (page 2 of the instant Office Action).

Anticipation under 35 U.S.C. § 102 requires that "every element of the claimed invention be identically shown in a single reference." (*In re Bond*, 910 F.2d 831,832 (Fed. Cir. 1990).

Applicant respectfully notes that the activating ligands of claim 6 are selected from the group consisting of human heregulin-β2, human heregulin-β2-like, human heregulin-β3, and human heregulin-γ, or a fragment thereof comprising a consecutive sequence of at least 10 amino acid residues of the corresponding heregulin sequence.

Carnahan does not discuss any of the above HER2 and/or HER3 receptor-activating ligands. For example, Applicants note that claimed fragments comprise a consecutive sequence of at least 10 amino acid residues of the corresponding heregulin sequence; however, the Carnahan hybrid α and β polypeptide does not include a consecutive sequence of at least 10 amino acid residues of a heregulin-β2, -β2-like, -β3, or -γ sequence. The activating ligands of the present claims do not include the Carnahan hybrid peptide, nor do they include recombinant rat or human NDFα2 peptides nor recombinant human NDFβ1 peptides discussed by Carnahan.

The subject matter of claim 6 being directed to activating ligands not discussed in Carnahan, Applicant respectfully submits that claim 6 is not anticipated by Carnahan. Accordingly, Applicant respectfully submits that the rejection of claim 6 under 35 U.S.C. § 102(e) is overcome and should be withdrawn.

The Rejection of Claim 9 under 35 U.S.C. §103(a)

Claim 9 stands rejected under 35 U.S.C. §103(a) as allegedly obvious over Carnahan in view of U.S. Patent 5,587,458 to King (hereafter, "King").

In order to establish a prima facie case of obviousness, there must be 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Carnahan is presented as discussing a method of stimulating inner ear cell growth using a (hybrid) heregulin polypeptide. The Examiner notes that Carnahan "does not teach the use of an agonist antibody" (Office Action mailed July 19, 2006, page 6, paragraph 11). The Examiner presents King as teaching the construction and

use of antibodies that bind and activate erbB2 (HER2), referring to the Abstract of the King reference.

However, neither Carnahan, King, nor the combination of Carnahan with King discuss or suggest heregulin agonist antibodies that are within claim 9. That is, neither Carnahan, King, nor the combination of Carnahan with King discuss or suggest heregulin agonist antibodies that are directed against heregulin polypeptides selected from the group consisting of heregulin-β2 (SEQ ID NO: 5), heregulin-β2-like polypeptide (SEQ ID NO: 9), heregulin-β3 (SEQ ID NO: 7), heregulin γ (SEQ ID NO: 11), heregulin-α (SEQ ID NO: 1) variants, heregulin-β1 (SEQ ID NO: 3) variants, heregulin-β2 (SEQ ID NO: 5) variants, heregulin-β2-like polypeptide (SEQ ID NO: 9) variants, heregulin-β3 (SEQ ID NO: 7) variants, heregulin γ (SEQ ID NO: 11) variants, heregulin-α (SEQ ID NO: 1) fragments, heregulin-β1 (SEQ ID NO: 3) fragments, heregulin-β2 (SEQ ID NO: 5) fragments, heregulin-β2-like polypeptide (SEQ ID NO: 9) fragments, heregulin-β3 (SEQ ID NO: 7) fragments, heregulin γ (SEQ ID NO: 11) fragments, heregulin agonist antibody and heregulin agonist antibody fragments, wherein said variants have at least 80% amino acid sequence identity with the corresponding heregulin sequence, and said heregulin fragments comprise a consecutive sequence of at least 10 amino acid residues of the corresponding heregulin sequence.

Moreover, King and Carnahan being directed to different arts, different cell types, and diametrically opposed goals, there is no suggestion or motivation in King to be combined with Carnahan. Being so opposed, and being directed to different ends, there is no reasonable expectation of success for such a combination, were it to be made. Moreover, since the two references are directed to such different, and opposed, ends, it appears that the only source for motivating such a combination would come from impermissible hindsight.

Since the combination of the cited references fails to provide all the elements of the subject claim, and since the cited references provide no motivation to combine the cited references to provide the claimed invention, nor any reasonable expectation of success were the references to be so combined, applicants respectfully submit that

claim 9 is not made obvious by the Carnahan in view of King. Accordingly, Applicants respectfully submit that the rejection of Claim 9 under 35 U.S.C. §103(a) is overcome.

The Rejection of Claim 11 under 35 U.S.C. §103(a)

Claim 11 stands rejected under 35 U.S.C. §103(a) as allegedly obvious over Carnahan in view of Carraway *et al.*, J. Biol. Chem. 269(19):14303-14306 (1994) (hereafter, "Carraway"). As noted above, claim 6 stands amended in the present Amendment; claim 11 depends from claim 6.

As discussed above, Carnahan is presented as discussing a method of stimulating inner ear cell growth using a (hybrid) heregulin polypeptide. The Examiner presents Carraway as providing rHRG-β1-177-244, "which is not specifically taught in the Carnahan patent" (page 7, lines 1-2 of the Office action mailed July 19, 2006).

However, Carraway provides no suggestion or motivation to use rHRG-β1-177-244 on inner ear cells; and Carnahan provides no suggestion or motivation to use a truncated portion of a recombinant β1 heregulin, alone and without linkage to a different heregulin sequence as well, in treatments of inner ear hair cells. In fact, there is not any such suggestion or motivation in the cited references themselves to combine the cited references to provide the claimed invention.

It appears that the Examiner feels that it would have been obvious to try the combination of Carnahan and Carraway. However, suggesting that it might have been obvious to try the claimed combination does not provide a case for obviousness. As stated by the Federal Circuit, "[O]bvious to try is not the standard." *Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 56 USPQ2d 1065 (Fed Cir. 2000) and "[W]e have consistently held that 'obvious to try' is not to be equated with obviousness under 35 USC 103." *Gillette Co. v. S. C. Johnson & Son, Inc.*, 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1997).

Lacking any suggestion or motivation to be combined, the cited references also fail to provide a reasonable expectation of success. Carnahan discusses hybrid artificial peptides that include sequences taken from different heregulins. However,

Carraway discusses rHRG-β1-177-244, which is derived from only a single heregulin. Canranhan's hybrid suggests that multiple sources of amino acid sequence might be required, yet Carraway has only one such source. Thus, the cited references teach away from the claimed invention, and provide no reasonable expectation of success that the rHRG-β1-177-244 polypeptide might be able to stimulate inner ear cell growth.

Accordingly, the cited references lacking any motivation or suggestion to be combined to provide the invention of claim 11, and lacking any reasonable expectation of success for such a combination, Applicants respectfully submit that the rejection of Claim 11 under 35 U.S.C. §103(a) is overcome.

The Rejections of Claims 1-5, 7, 8, 10-12, 14-17, and 19-21 under 35 U.S.C. §103(a)

Claims 1-5, 7, 8, 10-12, 14-17, and 19-21 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Carnahan in view of U.S. Patent 5,367,060 (hereafter "'060"). The USPTO presents the '060 patent as allegedly identifying fragments comprising amino acids 226-265 of both Hrg-α and Hrg-β as being preferred ligands with receptor binding affinity (page 5 of the instant Office Action).

Applicant notes that, before the present amendments, the claims previously recited fragments comprising amino acids 226-266; the '060 patent is presented as providing fragments comprising only amino acids 226-265, and thus lacking at least amino acid residue 266. However, Applicant has amended the present claims, deleting without prejudice the phrase "amino acids numbered 226 to 266", so that any discussion in the '060 patent of fragments is believed to be not relevant to the present claimed invention.

Accordingly, Carnahan, presented as discussing the use of hybrid fragments to stimulate utricular sensory epithelial cells, and the '060 patent each fail to provide the isolated ligands of the present claimed invention, and their combination fails to provide the isolated ligands of the present claimed invention. Moreover, the combination of the cited references provides no motivation to combine, nor reasonable expectation that

such a combination, if made, would provide the present invention with all the limitations of the pending claims.

Accordingly, the cited references lacking any motivation or suggestion to be combined to provide the invention of claim 11, and lacking any reasonable expectation of success for such a combination, Applicants respectfully submit that the rejections of claims 1-5, 7, 8, 10-12, 14-17, and 19-21 under 35 U.S.C. §103(a) is overcome.

CONCLUSION

In view of the foregoing, it is respectfully submitted that all claims in the present application stand in condition for allowance. Applicant respectfully requests reconsideration and allowance of all claims. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** referencing Attorney's Docket No. **39766-0035 C1**.

Respectfully submitted,

Date: February 21, 2007

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